ERECTILE DYSFUNCTION

Relation Between Erectile Dysfunction and Silent Myocardial Ischemia in Diabetic Patients: A Multidetector Computed Tomographic Coronary Angiographic Study

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ABSTRACT

Introduction: Erectile dysfunction (ED) can precede coronary artery disease. In addition, silent myocardial ischemia (SMI) is more common in diabetic patients and is a strong predictor of cardiac events and death.

Aim: To evaluate the presence of SMI in patients with diabetes and ED using multidetector computed tomographic coronary angiography (MDCT-CA).

Methods: This study evaluated patients with diabetes and ED without any history of cardiac symptoms or signs. Erectile function was evaluated with the Sexual Health Inventory for Men score, erection hardness score (EHS), and maximal penile circumferential change by an erectometer. MDCT-CA was used for the detection of coronary artery stenosis.

Main Outcome Measures: Sexual Health Inventory for Men score, EHS, maximal penile circumferential change, and coronary artery stenosis by MDCT-CA.

Results: Of 20 patients (mean age = 61.45 ± 10.7 years), MDCT-CA showed coronary artery stenosis in 13 (65%) in the form of one-vessel disease (n = 6, 30%), two-vessel disease (n = 2, 10%), and three-vessel disease (n = 5, 25%). Fifty percent of patients showed at least 50% vessel lumen obstruction of the left anterior descending coronary artery, which was the most commonly affected vessel (55%). Fifteen percent (3 of 20) of patients had greater than 90% stenosis, and two of them underwent an immediate coronary angioplasty with stenting to prevent myocardial infarction. Maximum coronary artery stenosis was positively correlated with age ($P = 0.016$, r = 0.529) and negatively correlated with EHS ($P = .046$, r = −0.449). Multivariate regression analysis using age and EHS showed that age was the only independent predictor of SMI ($P = .04$).

Conclusion: MDCT-CA can be a useful tool to identify SMI in diabetic patients with ED, especially in those of advanced age and/or with severe ED.

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Key Words: Diabetic Erectile Dysfunction; Silent Myocardial Ischemia; Multidetector Computed Tomographic Coronary Angiography

INTRODUCTION

Diabetes mellitus is a major public health problem around the world. It is estimated that the numbers of adults with diabetes will increase by 69% in developing countries and by 20% in developed countries from 2010 through 2030.[1] Most patients with diabetes (90—95%) have type 2 diabetes mellitus.[2] The death rate of diabetic adults is two to four times higher than for non-diabetic adults,[2] with cardiovascular disease (CVD) being the commonest cause of death.[3] The chronic hyperglycemia of diabetes is associated with macrovascular complications, including coronary artery disease (CAD), and microvascular complications that contribute to the pathogenesis of erectile

dysfunction (ED).[4] A recent systematic review has interpreted the link between CAD and ED as an interaction of several factors, including cardiovascular risk factors, androgens, and chronic inflammation, which can lead to endothelial dysfunction and atherosclerosis, suggesting ED and CAD might be two different presentations of the same systemic disease.[5]

The prevalence of ED in diabetic patients varies from 35% to 90%, with risk factors such as age, diabetes duration, glycemic control, sedentary lifestyle, smoking, and associated comorbidities.[6] A meta-analysis has associated ED with increased risk of CVD events in diabetic patients.[7] Even prediabetes identification in patients with ED has been associated with CVD predication.[8] Penile color Doppler ultrasound has been recognized as a potential tool for predicting silent myocardial ischemia (SMI) in patients with ED.[9]

Patients with SMI exhibit objective findings suggestive of myocardial infarction in the absence of angina or equivalent symptoms.[10] Although the prevalence of SMI is highly variable depending on the targeted population, age, and diagnostic tools, diabetes is associated with a marked increase in SMI prevalence.[11] Several studies have been conducted to screen for SMI in patients with diabetes using different tools with varying sensitivity and specificity,[12] including electrocardiography,[13,14] the ankle-brachial index,[15] nuclear myocardial perfusion imaging studies,[16−18] coronary artery calcium scoring using electron-beam computed tomography or multidetector computed tomography (MDCT),[19,20] or a combination of such tests.[21]

MDCT coronary angiography (MDCT-CA) has become a reliable non-invasive imaging modality with high specificity and sensitivity for the evaluation of CAD.[22,23] MDCT-CA has been used to screen patients with asymptomatic diabetes for SMI,[24] providing long-term prognostic value.[25] Some studies have used MDCT-CA to screen for SMI in patients with ED.[26−28] However, no previous studies have used MDCT-CA to screen patients with diabetes and ED.

AIM

This prospective study aimed to evaluate the presence of SMI in diabetic patients with ED using MDCT-CA.

METHODS

A prospective clinical study was conducted in diabetic men with ED seeking treatment at the Men's Health Clinic at Juntendo University Hospital (Tokyo, Japan) from March 2014 through March 2015. The inclusion criteria for the study were the absence of current and/or previous cardiac symptoms and signs. The study design was approved by the ethical and scientific research committee of Juntendo University Hospital (number 14-065). The ethical principles of the Declaration of Helsinki were followed and an informed consent was obtained from all patients. Diagnosis of diabetes was based on criteria of the American Diabetes Association 2013 guidelines.[29] Exclusion criteria included patients with cerebrovascular disease, congestive heart failure, congenital or valvular heart disease, cardiomyopathy, arrhythmia, advanced kidney (creatinine > 1.3 mg/dL) or liver disease, psychiatric disease, history of pelvic trauma, and pelvic surgery.

Initial Evaluation

History taking included a patient's personal history, special habits, duration and type of diabetes, associated medical diseases (hypertension, dyslipidemia), diabetic treatment, and ED history. History of chronic diabetic complications, including retinopathy and neuropathy, was obtained. General examination included weight, height, body mass index, and blood pressure.

Laboratory Investigations

Patients' glycemic control was evaluated by fasting blood glucose level, glycosylated hemoglobin level, and homeostasis model assessment of insulin resistance. Hemoglobin, high-sensitive C-reactive protein, prostate-specific antigen, and uric acid were evaluated because they could reflect cardiovascular risk burden. Diabetic nephropathy was evaluated by measuring albumin, urine β-microglobulins, serum creatinine, and estimated glomerular filtration rate. Patients with albuminuria (albumin > 30 mg/L) were considered to have nephropathy. A complete lipid profile, including triglyceride, very low-density lipoprotein cholesterol, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, ratio of total cholesterol to high-density lipoprotein cholesterol, apolipoprotein A_1, and apolipoprotein B, was obtained. Hormonal assessment of total and free testosterone, luteinizing hormone, and follicle-stimulating hormone levels was performed.

Erectile Function Evaluation

Patients' erectile function was evaluated by three validated tools. The first tool was the Sexual Health Inventory for Men (SHIM) questionnaire, which evaluated erectile function during the past 6 months. According to the SHIM score, patients were categorized as having mild ED (17−21), mild to moderate ED (12−16), moderate ED (8−11), or severe ED (1−7).[30] The second tool was the erection hardness score (EHS). According to the EHS, patients were categorized as having optimal erection (grade = 4), suboptimal erection (grade = 3), moderate ED (grade = 2), or severe ED (grade = 1).[31] The third tool was the maximal penile circumferential change (MPCC) using an erectometer (Nippon Medical Products, Asahikawa, Japan) during sleep for three nights. The MPCC measurement has a good correlation with the RigiScan[32] and EHS.[33] The ED cutoff point was an MPCC less than 20 mm, as reported in previous studies.[32]

Evaluation of SMI

A 64-row MDCT scanner (Sensation Cardiac 64; Somatom, Munich, Germany) was used to evaluate patients. Before MDCT

Table 1. Patients' clinical and laboratory characteristics (N = 20)*

Parameter	Mean ± SD, median (25th–75th percentile), or percentage	Range
History		
Age (y)	61.45 ± 10.7	42–81
Smoking	55	
Smoking history (y)	37 (14–47)	7–61
Cigarettes/d	20 (12.86–33.33)	1–100
Brinkman smoking index	848.18 ± 453.91	48–1,480
Diabetes duration (y)	6 (4–15)	1–20
ED history (y)	3 (2–7)	1–25
Hypertension	45	
Dyslipidemia	30	
Retinopathy	0	
Neuropathy	5	
Diabetes treatment: oral hypoglycemic/insulin	55/45	
General examination		
Weight (kg)	74.09 ± 17.04	32.6–114
Height (cm)	167.46 ± 5.82	159–179.7
BMI (kg/m^2)	26.33 ± 5.94	12.9–41.87
Systolic blood pressure (mmHg)	134 ± 14.17	120–164
Diastolic blood pressure (mmHg)	74.6 ± 7.89	60–88
Laboratory investigations		
Fasting blood glucose (mg/dL)	139.5 (121.5–189)	80–413
HbA1c (%)	7.38 ± 1.21	5.8–10.6
HOMA-IR (μU/mL)	15.55 (6.95–37.75)	1–104.8
hsCRP (mg/dL)	0.092 (0.021–0.461)	0.02–1.285
Hb (g/dL)	14.95 ± 1.32	12.8–17.7
PSA (ng/mL)	1.03 (0.47–1.63)	0.2–13.91
Uric acid (mg/dL)	5.94 ± 1.17	3.7–7.3
Albuminuria (mg/L)	20.65 (9.8–51.95)	6.5–1,403
Diabetic nephropathy	35	
Urine β_2-microglobulins (μg/L)	38 (29–113)	15–322
Creatinine (mg/dL)	0.77 ± 0.2	0.44–1.11
Estimated glomerular filtration rate (mL/min/1.73 m^2)	89.26 ± 26.9	49.5–140
Triglyceride (mg/dL)	157.98 ± 91.05	46–424
VLDL cholesterol (mg/dL)	31.58 ± 18.21	9.2–71.6
Total cholesterol (mg/dL)	178 ± 36.88	117–271
HDL cholesterol (mg/dL)	44.24 ± 9.35	27–59
Total cholesterol/HDL ratio	3.7 (3.4–4.9)	2.98–6.69
LDL cholesterol (mg/dL)	104.06 ± 23.68	60–144
Apolipoprotein A$_1$ (mg/dL)	143.8 ± 23.23	111–191
Apolipoprotein B (mg/dL)	92.47 ± 11.96	65–110
Total testosterone (ng/mL)	5.53 ± 2	2.99–10
Free testosterone (pg/mL)	7.75 ± 2.46	4–13.8
LH (mIU/mL)	6.1 (5.1–7.7)	1.8–27.34
FSH (mIU/mL)	8.66 (7.4–11.45)	3.3–50.03
Erectile function evaluation		
SHIM score	5 (2.5–8.5)	1–16
EHS	2 (1–2)	1–3
MPCC (mm)	14.5 ± 9.46	2.33–32

BMI = body mass index; ED = erectile dysfunction; EHS = erection hardness score; FSH = follicle-stimulating hormone; Hb = hemoglobin; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; hsCRP = high sensitive C-reactive protein; LDL = low-density lipoprotein; LH = luteinizing hormone; MPCC = maximal penile circumferential change; PSA = prostate-specific antigen; SHIM = Sexual Health Inventory for Men; VLDL = very low-density lipoprotein.

*Variables with a normal distribution are expressed as mean ± SD. Variables not normally distributed are expressed as median (25th–75th percentile). Categorical variables are expressed as percentage. The Shapiro-Wilk test was used for testing the normality of the variables.

Table 2. Results of multidetector computed tomographic coronary angiography (N = 20)*

Parameter	Grades	n (%)
MDCT-CA result	Positive coronary artery stenosis	13 (65)
MDCT-CA according to CAD obstruction	Non-obstructive CAD (<50%)	3 (15)
	Obstructive CAD (≥50%)	10 (50)
Quantitative MDCT-CA stenosis grading	Minimal (<25%)	1 (5)
	Mild (25–49%)	2 (10)
	Moderate (50–69%)	3 (15)
	Severe (70–99%)	7 (35)
	Severe (≥90%)	3 (15)
MDCT-CA according to number of affected vessels	1-vessel CAD	6 (30)
	2-vessel CAD	2 (10)
	3-vessel CAD	5 (25)
MDCT-CA according to affected vessels	RCA	7 (35)
	LMT	2 (10)
	LAD	11 (55)
	LCX	6 (30)

CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LMT = left main trunk coronary artery; MDCT-CA = multidetector computed tomographic coronary angiography; RCA = right coronary artery.
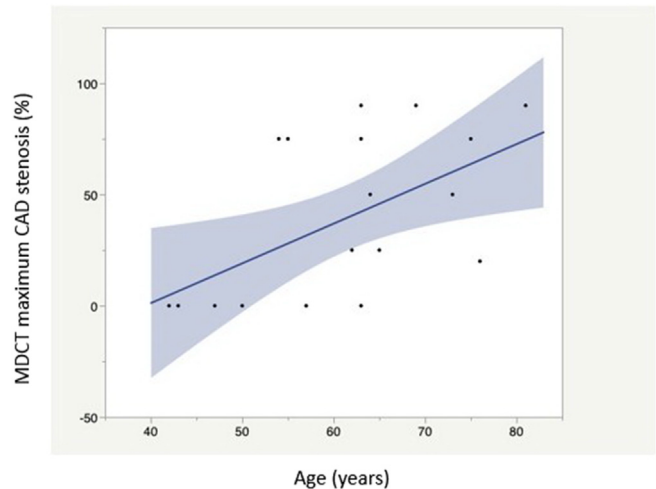*Data are expressed as number of patients (percentage).

Figure 1. Correlation between MDCT maximum coronary artery stenosis and age using the Pearson correlation test ($P = 0.016$, $r = 0.529$). CAD = coronary artery disease; MDCT = multidetector computed tomography.

regression analysis using age and EHS was performed. JMP 11.0 (SAS Institute, Cary, NC, USA) was used for data analysis. A P value less than .05 was considered significant.

MAIN OUTCOME MEASURES

The main outcome measurements were the SHIM score, the EHS, MPCC, and coronary artery stenosis by MDCT-CA.

RESULTS

The study included 20 patients with diabetes and ED (mean age = 61.45 ± 10.7 years). Most patients had type 2 diabetes (95%) for a median of 6 years (range = 1–20 years). Associated comorbidities were smoking (55%), hypertension (45%), and dyslipidemia (30%). All data related to the patients' characteristics, including history, general examination, laboratory investigations, and erectile function, are presented in Table 1. Erectile function evaluation according to the SHIM score was 5 (range = 1–16); 75% had severe ED (score ≤ 7) and 25% had mild to moderate (score = 12–16) or moderate (score = 8–11) ED. The patients' EHS was 2 (range = 1–3), and 78.9% of patients had an EHS no higher than 2. The MPCC was 11.66 (range = 2.33–32), and 64.3% of patients had an MPCC less than 20 mm.

MDCT-CA showed positive coronary artery stenosis in 65% of subjects. Fifty percent of patients showed obstructive CAD (≥50% lumen obstruction). One-vessel CAD (30%) was the commonest presentation. The left anterior descending coronary artery was the commonest coronary artery with stenosis. Data related to MDCT-CA are presented in Table 2. Fifteen percent (3 of 20) of patients had greater than 90% stenosis, and two of them underwent an immediate coronary angioplasty with stenting to prevent myocardial infarction. Maximum coronary
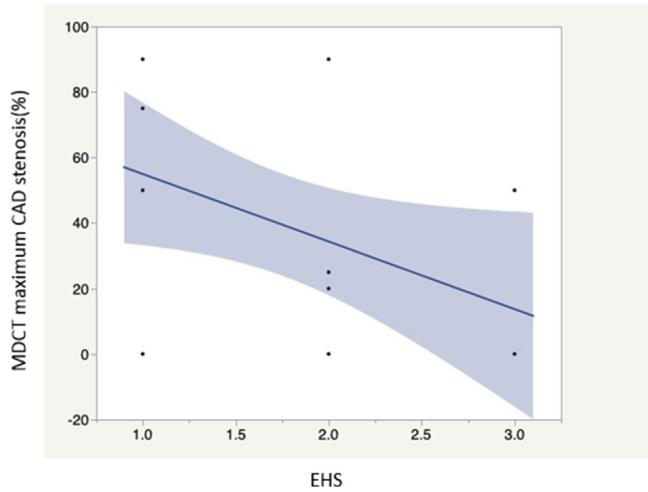
scanning, oral metoprolol was administrated to patients to slow their heart rates to lower than 70 beats/min. After electrocardiographic electrodes were connected, patients were asked to hold their breath during the scan. The scan parameters included 0.5-mm slices thickness, 120-kV tube voltage, and 500-mA tube current. MDCT-CA results were evaluated as the presence (positive) or absence (negative) of coronary artery stenosis. Quantitative grading of maximum coronary artery stenosis as minimal (<25%), mild (25–49%), moderate (50–69%), and severe (70–99%) was performed as recommended by the Society of Cardiovascular Computed Tomography.[34] Patients with coronary artery stenosis were classified according to the decrease in luminal diameter as having obstructive CAD (≥50%) or non-obstructive CAD (<50%).[35] The number of stenotic vessels (one, two, or three) was estimated. Also, coronary artery stenosis was classified according to coronary artery nomenclature (right, left main trunk, left anterior descending, and left circumflex coronary arteries). Patients with positive MDCT-CA results were informed and followed up (follow-up data incomplete).

Statistical Analysis

Correlations between age and maximum stenosis by MDCT-CA and between EHS and maximum stenosis by MDCT-CA were performed using the Pearson correlation test with a two-tailed P value. To identify predictors of SMI, multivariate

Figure 2. Correlation between MDCT maximum coronary artery stenosis and EHS using the Pearson correlation test ($P = 0.046$, $r = -0.449$). CAD = coronary artery disease; EHS = erection hardness score; MDCT = multidetector computed tomography.

artery stenosis was positively correlated with age ($P = .016$, $r = 0.529$; Figure 1) and negatively correlated with EHS ($P = .046$, $r = -0.449$; Figure 2). Multivariate regression analysis using age and EHS showed that age was the only independent predictor for SMI ($P = .04$; Table 3). A representative MDCT-CA result of one patient is shown in Figure 3.

DISCUSSION

The present study examined the magnitude of the effect of ED on cardiovascular status in diabetic patients using the non-invasive diagnostic modality of MDCT-CA. The present study is the first to use MDCT-CA in patients with asymptomatic diabetes and ED; other studies have used MDCT-CA to investigate patients with only diabetes[24,25] or patients with only ED.[26–28] For the relation between ED and CAD, Montorsi et al[35] proposed the artery size hypothesis, which states that when the penile arteries are smaller (1–2 mm) than the coronary arteries (3–4 mm), the penile vasculature is affected sooner by cardiovascular risk factors, which makes ED a predictor of CVD events. The association between ED and CVD events is well established,[36] especially in diabetic patients.[37] Therefore, ED should be considered an independent CVD risk until proved otherwise.[38]

In the present study, MDCT-CA depicted coronary artery stenosis in 65% of patients with ED and asymptomatic CAD. The rate of CAD in diabetic patients with concomitant ED is controversial. One study of patients with asymptomatic diabetes screened with MDCT-CA showed stenosis in 36.5% (19 of 52).[24]

The present study found that SMI was very common in diabetic patients with ED without any cardiac symptoms and signs. It showed that 50% of patients had significant obstructive CAD (≥50% decrease in vessel lumen) and 25% of patients had three-vessel CAD. This is considered an alarming sign because

Table 3. Multivariate regression analysis to identify predictors of silent myocardial ischemia using age and EHS parameters

Variable	Sum of square	F ratio	P value
Age	4,439.132	4.932	.0402
EHS	2,483.168	2.759	.1150

EHS = erection hardness score.

obstructive CAD and three-vessel CAD were reported as predictors of all cardiac events after more than 5 years of follow-up of 405 diabetic patients.[34] In addition, left anterior descending coronary artery stenosis was reported in 55% of patients, which was associated with worst prognosis among other myocardial infarction types owing to a larger infarct, especially with advanced age.[39] Therefore, ED identification, especially in diabetic patients younger than 60 years, could assist in CVD risk evaluation and decrease the risk of an event.[40]

A significant positive correlation was observed between ED severity and maximum coronary artery stenosis by MDCT-CA in diabetic patients. The present results are supported by studies that used MDCT-CA to screen patients with ED.[26,28] In diabetic patients, increasing ED severity was associated with increased total CVD risk,[41] with poor CVD prognosis.[42] Therefore, ED could be used as a warning sign for SMI. The leading interval from ED to CVD events was estimated at 2 to 5 years.[43] In diabetic patients, ED is a predictor of CAD and cardiac events, with a 1.4-fold higher CAD risk compared with diabetic patients without ED.[44] Therefore, ED in diabetic patients is considered an atherosclerosis marker that could assist in the detection of subclinical vascular disorders.[45] In patients with diabetes and ED, SMI has been screened using different stress tests,[46–48] showing that the presence vs absence of ED can improve the sensitivity of screening guidelines for SMI in diabetic patients.[49]

In the present study, age was the only predictor for coronary artery stenosis in diabetic patients with ED. This result is consistent with that of a study that showed that increasing age was an independent risk factor for a high Agatston coronary artery calcium score in patients with ED.[28] In another study, ED predicted CAD in patients with type 2 diabetes without clinically evident CVD.[50] A prospective study found that predictors of SMI were diabetes duration, intima-media thickness, and statin therapy at MDCT-CA screening of patients with asymptomatic diabetes.[24] Recently, MDCT-CA screening of 320 patients with asymptomatic diabetes showed that a glycosylated hemoglobin level of at least 7.4%, dyslipidemia, diabetes duration, and retinopathy were predictors for SMI.[51] Therefore, MDCT might be helpful to identify CAD in diabetic patients with ED and high risk for CVD (including aging) in the future. Radiation exposure from these screening modalities also should be considered.

The present study has several limitations. The sample was extracted from outpatients who presented at our clinic seeking for treatment for ED. Thus, the subjects were from a strongly biased population. Furthermore, we could not set the controls; therefore,
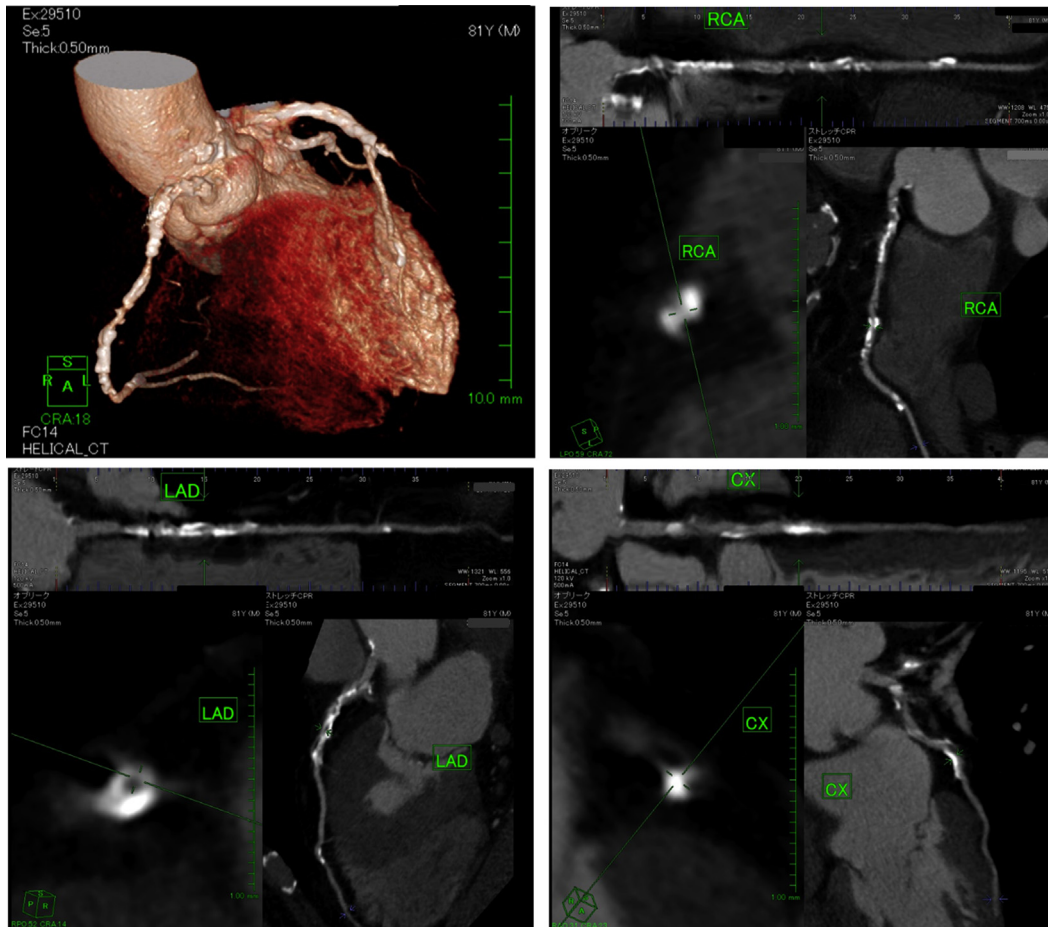
Figure 3. Representative multidetector computed tomographic coronary angiographic result showing stenosis of the RCA, LAD, and CX in an 81-year-old man with diabetes and erectile dysfunction. CX = left circumflex coronary artery; LAD = left anterior descending coronary artery; RCA = right coronary artery.

we could not compare the CAD prevalence in diabetic patients with ED with other combinations of disease status, such as subjects with vs without diabetes and/or with vs without ED. Comparative data on CAD prevalence in diabetic patients are needed. In addition, CAD should be assessed separately for type 1 and for type 2 diabetes owing to different pathogeneses and outcomes. The sample size was limited; therefore, only two parameters (age and ED severity) were used to assess the predictive factor for SMI. We did this to distinguish the stronger predictor for CAD, and we believe this information is important for patients with diabetes and ED. The diagnosis of CAD in diabetic patients with ED was performed using only MDCT-CA, which is an indicator of atherosclerosis but cannot assess inducible ischemia as stress testing can. Also, coronary artery calcium scoring was not calculated for the MDCT-CA scan because we used coronary artery stenosis grading as an outcome measurement for the MDCT-CA results. In the future, a large-scale comparative study including healthy men should be performed.

CONCLUSIONS

CAD was highly prevalent (65%) in diabetic patients with ED in our outpatient clinic. Furthermore, 15% of patients showed severe coronary artery stenosis ($\geq$90%), which might lead to myocardial infarction. Age was the single significant predictor for coronary artery stenosis in diabetic patients with ED. One should consider the possibility of SMI in elderly patients with diabetes who have ED.

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